CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022460Orig1s000

PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	22-460
SERIAL NUMBER:	000
DATE RECEIVED BY CENTER:	20 March 09
PRODUCT:	[dutasteride/tamsulosin combination product]
INTENDED CLINICAL POPULATION:	men with BPH
SPONSOR:	GlaxoSmithKline
DOCUMENTS REVIEWED:	EDR
REVIEW DIVISION:	Division of Reproductive and Urologic Products (HFD-580)
PHARM/TOX REVIEWER:	Laurie McLeod-Flynn, Ph.D., D.A.B.T.
PHARM/TOX SUPERVISOR:	Lynnda Reid, Ph.D.
DIVISION DIRECTOR:	Scott Monroe, M.D.
PROJECT MANAGER:	Olga Salis

Date of review submission to Division File System (DFS): 18 November 2009

EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability: There is no impediment to approval from a pharmacology/toxicology perspective.

B. Recommendation for nonclinical studies: None at this time.

C. Recommendations on labeling

Proposed labeling: (proposed changes in red and ~~strikethrough~~)

(b) (4)

2 Page(s) has (have) been Withheld in Full immediately following this page as B4 (CCI/TS)

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings: No new nonclinical toxicology studies were submitted with this application.

B. Pharmacologic activity: Dutasteride is a competitive 5-alpha-reductase antagonist. Tamsulosin, is an alpha-1-adrenoceptor antagonist. A battery of *in vitro* assays revealed no evidence of overlapping primary or secondary pharmacological activity which would be of concern with regard to this combination of drugs.

C. Nonclinical safety issues relevant to clinical use: No new toxicology studies and no nonclinical studies of this drug combination were submitted. Nonclinical safety issues relevant to clinical use have been previously identified for dutasteride and are adequately described in the previous and proposed labeling i.e. the specific teratogenicity of dutasteride in animal studies at less than clinical exposure levels and the neurotoxicity in animal studies at very high exposures.

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 22460
Review number: 1
Sequence number/date/type of submission: 000 / 20 March 09 / original NDA
Information to sponsor: Yes ( ) No (x)
Sponsor and/or agent: GlaxoSmithKline

Manufacturer for drug substance: GlaxoSmithKline and (b) (4)

Reviewer name: Laurie McLeod-Flynn
Division name: Division of Reproductive and Urologic Products
HFD #: 580
Review completion date: 22 October 2009

Drug:

Trade name: (b) (4)
Generic name: Dutasteride and Tamsulosin
Chemical name:

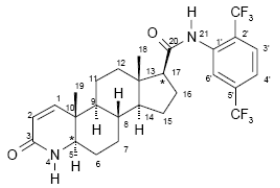
Dutasteride: (5α,17β)-N-{2,5 bis(trifluoromethyl) phenyl}-3-oxo-4-azaandrost-1-ene-17-carboxamide
Tamsulosin: *R(-)*-5-[2-[[2-(2-Ethoxyphenoxy)ethyl]amino]propyl]-2-methoxybenzene sulfonamide, monohydrochloride

Molecular formula/molecular weight:

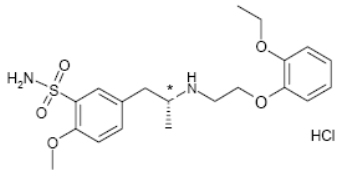
Dutasteride: $C_{27}H_{30}N_2F_6O_2$/ 528.54
Tamsulosin: $C_{20}H_{28}N_2O_5S \bullet HCl$/ 444.97

Structure:

Dutasteride:



Tamsulosin:



Relevant INDs/NDAs/DMFs: NDA 21319

Drug class:

Dutasteride: 5-alpha-reductase antagonist
Tamsulosin: alpha-1-adrenoceptor antagonist

Intended clinical population: men with BPH

Clinical formulation:

Composition of DTC, 0.5 mg Dutasteride and 0.4 mg Tamsulosin Hydrochloride

Component	Quantity (per capsule)	Function	Reference to Standard
Dutasteride Product Intermediate	1 each	Active	GlaxoSmithKline
Tamsulosin Hydrochloride Product Intermediate [1]	(b) (4)	Active	GlaxoSmithKline
Pre-printed (b) (4) Hard-Shell Capsule	1 each	Capsule Shell	Supplier

Composition of the Dutasteride Product Intermediate, 0.5 mg

Component	Quantity (mg/capsule)	Function	Reference to Standard
Fill Solution			
Dutasteride [1]	0.50	Active	GlaxoSmithKline
Mono-di-glycerides of Caprylic/Capric Acid (MDC) [1]	(b) (4)		Supplier
Butylated Hydroxytoluene (BHT)			USNF
(b) (4)			-
Gelatin			USNF
Glycerin			USP
Titanium Dioxide			USP
Ferric Oxide, Yellow [2]			USNF
(b) (4)			USP
			-
			Ph.Eur.
			USNF

Note:
1. (b) (4)
2. Ferric Oxide is also referred to as Iron Oxide Yellow
3. (b) (4)
4.

Composition of the Tamsulosin Hydrochloride Product Intermediate, 0.4 mg Tamsulosin Hydrochloride

Component	Quantity (mg/capsule)	Function	Reference to Standard
(b) (4)			
Tamsulosin Hydrochloride [1]	0.400	Active	Supplier
Microcrystalline Cellulose	(b) (4)		USNF
Methacrylic Acid Copolymer Dispersion [2]			USNF
Talc			USP
Triethyl Citrate			USNF
(b) (4)			USP
			-
Methacrylic Acid Copolymer Dispersion [2]			USNF
Talc			USP
Triethyl Citrate			USNF
(b) (4)			USP
			-
			-

Note: (b) (4)

Composition of the Pre-printed (b) (4) Hard-Shell Capsule, Body and Cap[1]

Component	Quantity (mg per 100 mg)		Reference to Standard
	Brown Body [2]	Orange Cap [2]	
Carrageenan	(b) (4)		USNF
Potassium Chloride			USP
Titanium Dioxide			USP
Ferric Oxide, Red [4]			USNF
FD&C Yellow 6			-
(b) (4)			USP
Hypromellose			USP
Black Ink [1, 5]			Supplier
(b) (4)			USNF USNF

Note:
1. Information relating to these (b) (4) hard-shell capsules including printing ink is provided via DMF (b)
2. (b) (4) capsule shell body and cap weight ratio is approximately (b) respectively.
3. (b) (4)
4. The amount of ferric oxide, red does not exceed (b) (4)
5. (b) (4) Black Ink or (b) (4) Black Ink.
6. The typical amount of (b) (4) per capsule is approximately (b) ppm per capsule.
7. The typical amount of (b) (4) is approximately (b) (4) ppm per capsule.

Route of administration: oral

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Data reliance: Except as specifically identified below, all data and information discussed below and necessary for approval of NDA 22460 are owned by GlaxoSmithKline or are data for which GlaxoSmithKline has obtained a written right of reference. Any information or data necessary for approval of NDA 22460 that GlaxoSmithKline does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that GlaxoSmithKline does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA 22460.

Studies reviewed within this submission:

An in vitro preclinical profile of GIl38525A (Tamsulosin) at a range of 7-transmembrane Receptors (Glaxo, 2007).

The preclinical in vitro profile of GI138525A (Tamsulosin) at a selection of 7 transmembrane monoamine receptors (Glaxo, 2006).

Tamsulosin (GI138525A) has low affinity for the human hERG channel (Glaxo, 2007).

PHARMACOLOGY

Study title: The preclinical *in vitro* profile of GI138525A (Tamsulosin) at a selection of 7 transmembrane monoamine receptors (Glaxo, 2006).

In agreement with published literature, GI138525A had high affinity and profiled as an antagonist at the alpha1A and alpha1B adrenoreceptors with fpKi's of ~10.3 and 9.8, respectively.

GI138525A was inactive in these agonist assays: A_{2a} pEC_{50} <4.5, A_{2b} pEC_{50} <4.5.

GI138525A was inactive in these antagonist assays: A_{2b} pKi <5.2, EP_4 pKi <5.2, H_3 fpKi <6.2.

GI138525A was active in these agonist assays; D_2 short pEC_{50} 8.2, D_4 pEC_{50} 7.5, 5-HT_{1A} pEC_{50} 8.6, 5-HT_{1B} pEC_{50} 6.5.

GI138525A was active in these antagonist assays: D_2 long fpKi 7.8, D_3 fpKi 8.7, D_4 fpKi 7.4, H_1 fpKi range 5.3-6.0 for two technologies.

These results indicate that GI138525A has measurable activity at a range of receptors with the following fold selectivity when compared to the primary alpha 1A adrenoreceptor antagonist data.

Less than 10 fold- alpha 1B (ant)
Between 10 and 100 fold - 5-HT_{1A} (ag), D_3 (ant)
Greater than 100 fold -Adenosine A_{2a} (ag), Adenosine A_{2b} (ag/ant), Dopamine D_2 (ag (S)/ant (L)), D_4 (ag/ant), EP_4 (ant), 5-HT_{1B} (ag), histamine H_1 (ant), H_3 (ant).

Study title: An in vitro preclinical profile of GIl38525A (Tamsulosin) at a range of 7-transmembrane receptors (Glaxo, 2007).

GI138525A had high affinity at the human a1pha1A, a1phalB and a1phalD adrenoreceptors with pKi's of ~10.2, 9.2 and 9.8, respectively.

GI138525A was inactive in these human receptor binding assays: a1pha2C pIC_{50} <4.8, CCR5 pIC_{50} <4.5, ga1anin pIC50 <4.4, glucagon pIC_{50} <4.5, NPYl pIC_{50} <4.5, NPY2 pIC_{50} <4.5, NPY4 pIC_{50} <4.5, NPY5 pIC_{50} <4.5, orexin1 pIC_{50} <4.5.

GI138525A was inactive in agonist assays at the following human receptors: beta1 pEC_{50} <4.5, beta2 pEC_{50} <4.5, beta3 pEC_{50} <4.5, CT2 pEC_{50} <4.5, EP2 pEC_{50} <4.5, GLP1 pEC_{50} <4.5, MC1 pEC_{50} <4.5, MC3 pEC_{50} <4.5, MC4 pEC_{50} <4.5, MC5 pEC_{50} <4.5, PTHl pEC_{50} <4.5, CCR3 pEC_{50} <4.5, orexin2 pEC_{50} <4.5.

GI138525A was inactive in an antagonist assay at the following human receptor: MCH

pIC_{50} <4.5.

GI138525A was inactive in the following animal ortho1ogue agonist assays: hamster CT2 pEC_{50} <4.5 and against frog melanophore endogenous receptors coupled via Gi, Go or Gs all pEC_{50} <4.5.

GI138525A was inactive in the following animal ortho1ogue antagonist assay: hamster thrombin pIC_{50} <4.5.

GI138525A was active in these binding assays: a1pha2A pEC_{50} 6.4, alpha 2B pEC_{50} 6.4.

These results indicate that GI138525A has measurable activity at some of the range of human receptors tested with the following fold selectivity when compared to the primary alpha 1 A adrenoreceptor binding data.

Less than 10 fo1d- a1pha1D
Between 10 and 100 fold - a1phalB
Nearly 6000 fold - a1pha2A and a1pha2B
Greater than 10000 fold - a1pha2C (binding), CCR5 (binding), ga1anin (binding), glucagons (binding), NPY1 (binding), NPY2 (binding), NPY 4 (binding), NPY5 (binding), orexin1 (binding), betal (agonist), beta2 (agonist), beta3 (agonist), CT2 (agonist), EP2 (agonist), GLPl (agonist), MC1 (agonist), MC3 (agonist), MC4 (agonist), MC5 (agonist), PTH1 (agonist), CCR3 (agonist), orexin2 (agonist), MCH (antagonist).

Safety pharmacology

Study title: Tamsulosin (GI138525A) has low affinity for the human hERG channel (Glaxo, 2007).

Tamsulosin (GI138525A) was tested in a binding assay at the human hERG ion channel. The compound displaced the radioligand ([^{3}H]-dofetilide) at pIC_{50} 4.8$\pm$0.2 (n=64). The asymptote of the curve fit was 99$\pm$7%, consistent with complete displacement.

Tamsulosin was also tested in an FP binding assay (n=2) with a pIC_{50} of 4.6.

Conclusion: A battery of *in vitro* assays revealed no evidence of overlapping primary or secondary pharmacological activity which would be of concern with regard to this combination of drugs.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22460	ORIG-1	SMITHKLINE BEECHAM CORP DBA GLAXOSMITHKLINE	DUTASTERIDE/ TAMSULOSIN HYDROCHLORIDE

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LAURIE L MCLEOD FLYNN
11/18/2009

LYNNDA L REID
11/18/2009

I concur with Dr. McLeod-Flynn's review of NDA 22-460:
- there are no outstanding safety issues with this combinaton product
- proposed draft labeling

Nonclinical data support approval.